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5 PREPARATION AND COMPOSITION OF INTER-ALPHA INHIBITOR PROTEINS FROM
HUMAN PLASMA FOR THERAPEUTIC USE

RELATED APPLICATION

10 This application contains subject matter that is related to that disclosed in provisional
patent application Ser. No. ^{60/518,346}~~60/~~ filed November 8, 2003, entitled, "Preparation and
Composition of Inter-alpha Inhibitor Proteins from Human Plasma for Therapeutic Use," the
disclosure of which application is incorporated herein in its entirety by this reference.

GOVERNMENT SUPPORT

15 A portion of this invention may have been supported by National Institutes of Health
grants RO1 GM053008, R01 GM057468, and R43 GM065667.

BACKGROUND OF THE INVENTION

20 The inter-alpha inhibitor protein (α_1 I_p) family is a group of plasma-associated serine
protease inhibitors. Members of this family are composed of heavy and light polypeptide
subunits that are covalently linked by a glycosaminoglycan. The light chain, also called bikunin,
is responsible for the serine protease inhibitory activity of the molecules. The name "bikunin"
reflects the presence of 2 protease-inhibiting domains of the Kunitz type. In normal plasma,
bikunin is found mostly in a complex form as inter-alpha inhibitor (α_1 I), which has a molecular
25 weight of 225 kDa, and pre-alpha inhibitor (α_1 I_p), which has molecular weight of 120 kDa. In
 α_1 I, bikunin is linked to 2 heavy polypeptide chains, H1 and H2, whereas, in α_1 I_p, only a single
heavy chain (H3) is linked to bikunin. In these complexed forms, bikunin remains inactive until
its release by partial proteolytic degradation, a mechanism that serves as a means to regulate
activity. After cleavage from the complex, the activated bikunin is cleared rapidly from plasma
30 by glomerular filtration, a process that is facilitated by its low molecular weight and by receptor-
mediated uptake. US Patent Nos. 6,489,128 and 6,660,482 are related to the use of diagnosing
cancer and sepsis, respectively. Methods of inhibiting metastases and of treating sepsis are also